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Multiple Sclerosis-Related Trigeminal Neuralgia: A Prospective Series of 43 Patients Treated with Gamma Knife Surgery with More than One Year of Follow-Up

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Key Words
Multiple sclerosis · Trigeminal neuralgia · Gamma knife radiosurgery

Abstract
Background: Trigeminal neuralgia (TN) related to multiple sclerosis (MS) is more difficult to manage pharmacologically and surgically. ***Objective:*** This article aims to evaluate the safety and efficacy of Gamma Knife surgery (GKS) in this special group of patients. ***Methods:*** Between July 1992 and November 2010, 43 cases with more than 1 year of follow-up were operated with GKS for TN related to MS and prospectively evaluated in the Timone University Hospital, Marseille, France. Radiosurgery using the Gamma Knife (model B or C or Perfexion) was performed. A single 4-mm isocenter was positioned at a median distance of 8 mm (range 5.7–14.7) anterior to the emergence of the nerve. A median maximum dose of 85 Gy (range 75–90) was delivered. ***Results:*** The median follow-up period was 53.8 months (12–157.1). Thirty-nine patients (90.7%) were initially pain free. Their actuarial probability of remaining pain free without medication at 6 months, 1, 3, 5 and 10 years was 87.2, 71.8, 43.1, 38.3 and 20.5%, respectively, and remained stable till 12 years. The hypoesthesia actuarial rate at 6 months, 1 and 2 years was 11.5, 11.5 and 16%, and remained stable till 12 years. ***Conclusions:*** GKS proved safe and effective in this special group of patients.

Introduction

Trigeminal neuralgia (TN), also known as 'tic douloureux', is a serious health problem, with a prevalence rate of 4–5 per 100,000 people [1]. The association of TN and multiple sclerosis (MS) has been known since the end of the 19th century [2]. The pathophysiology is considered related to a demyelination phenomenon involving the trigeminal nerve. Trigeminal pain has usually the same features and the same chronic and paroxysmal pain characteristics as classical TN (CTN), except for the fact that it is more frequently bilateral. Burchiel and Slavin [3] classified the MS-related TN as symptomatic. TN secondary to MS is additionally more often difficult to manage pharmacologically and surgically, with lower response rates than CTN [4–6].

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The number of articles reporting the safety and efficacy of Gamma Knife surgery (GKS) in TN has continually increased since 1996 [7]; however, only 5 dedicated studies about the role of GKS in MS-related TN are available up-to-date [8–12]. Furthermore, the number of patients and their follow-up in published series are limited.

We report a single-institution experience in the Timone University Hospital, Marseille, France. We prospectively assessed the initial pain cessation, hypoesthesia and recurrence actuarial rates. The present series has the biggest number of cases in the current literature, with a very long-term follow-up.

Methods

Patient Population and Selection

Between July 1992 and November 2010, 737 patients presenting with intractable TN were treated with GKS and followed up prospectively in the Timone University Hospital in Marseille, France. Patients fulfilling the criteria of the International Headache Society (2003) [13] were accepted for treatment.

Evaluation of the type of trigeminal pain was made according to the classification proposed by Eller et al. [14] into idiopathic TN1 and TN2. While TN1 is described as typically sharp, shooting, electrical shock-like, with pain free intervals between the attacks, TN2 is described as an aching, throbbing or burning pain, for more than 50% of the time and constant in nature (constant background pain being the most significant attribute). Of these patients, 57 (7.7%) had a MS-related TN. We further selected for analysis 43 cases with more than 1 year of follow-up.

Radiosurgical Technique

During the 18 years of the study, various models of the Gamma Knife were used (models B, C, 4C or Perfexion, Elekta Instruments Inc.). After application of the Leksell Model G stereotactic frame (Elekta Instruments) under local anesthesia, all patients underwent stereotactic magnetic resonance imaging (MRI) and computer tomography (CT scan) to identify the trigeminal nerve. The MRI sequences used are T2-weighted type CISS (Siemens) without contrast and contrast-enhanced T1-weighted images. CT scans routinely supplement the neuroradiological investigation in order to correct any distortion errors on the MRI images [15].

In the Gamma Unit in Marseille, France, we use the anterior target, which means placing a unique isocenter on the cisternal portion of the trigeminal nerve using a very anterior target, located immediately posterior to the gasserian ganglion, as described previously [15, 16], at a median distance (if possible) of approximately 7.5 mm from the entry of the trigeminal nerve into the brainstem, if the anatomical conditions allow this. We initially give a dose of 90 Gy at the 100% isodose. Beam channel blocking is used depending on the dose received by the first 10 mm^3 of the brainstem: should this dose be more than 15 Gy, we diminish the dose and start plugging so as to be able to avoid increasing the length of the treated nerve which could account for more toxicity (the so-called 'Flickinger effect') [15].

A single 4-mm isocenter was used for all 43 patients (100%) and was positioned in the cisternal portion of the trigeminal nerve at a median distance of 8 mm (range 5.7–14.7) anterior to the entrance of the trigeminal nerve into the brainstem.

A median maximum dose of 85 Gy (range 75–90) was delivered. Further analysis of the maximum doses revealed 40 available data with 2 patients (4.6%) receiving 75 Gy, 7 patients (16.3%) receiving 80 Gy, 17 patients (39.5%) receiving 85 Gy and 14 patients (32.5%) receiving 90 Gy, respectively. So, overall, 88.3% of the patients received a maximum dose of at least 80 Gy in this series.

Patients continued their medication unchanged for 1 month after GKS and then were able to reduce the drug doses depending on the treatment efficacy. We usually evaluated these patients for a neurological examination including facial sensibility and motility and corneal reflex at 3 months, 6 months and 1 year after the treatment and then regularly once a year.

A team consisting of a neurosurgeon, radiation oncologist and a medical physicist performed dose selection and planning.

Follow-Up and Assessment of Outcome

The Université de la Méditerranée and the Direction and the Ethical Committee of the Timone University Hospital (CPPRB 1) approved our study. Follow-up information was obtained in two ways: direct clinical evaluation or telephone interview by the first author (C.T.) who was not involved in the selection of the cases for treatment.

We evaluated the initial pain cessation, the onset of the sensory disturbance and the recurrence. We analyzed the data regarding the latency intervals to achieve the features, making sure to date every event, the use of medication and the need for surgical procedures, so as to accurately assess all the information available.

Pain was scored using 3 different scales: Barrow Neurological Institute scale (BNI; class I: no trigeminal pain, no medication; II: occasional pain, not requiring medication; IIIa: no pain, continued medication; IIIb: controlled with medication; IV: some pain, not adequately controlled with medication; V: severe pain, no pain relief), Burchiel (class I: pain free, no medication; II, pain free on medication; IIIa: pain improved, no medication; IIIb: pain improved, on medication; IV: pain not improved) and Regis (class I: no trigeminal pain, no medication; II: no pain, with medication; III: pain frequency reduction >90%; IV: pain frequency reduction 50–90%; V: no pain reduction; VI: pain worsening) [14, 16, 17].

For hypoesthesia evaluation, we used the BNI facial hypoesthesia scale (class I: no facial numbness; II: mild facial numbness, not bothersome; III: facial numbness, somewhat bothersome; IV: facial numbness, very bothersome) [17]. For patients presenting facial sensory dysfunction, we also inquired about their quality of life related to TN and whether this sensory problem was bothering them or not. We furthermore asked whether or not they had mastication difficulties.

The patients and referring doctors were instructed to continue the medication unchanged for at least 1 month and then it was suggested to reduce the drug doses progressively if they were pain free. A case report form was created and filled in prospectively as from the first patient. The initial follow-up was based on clinical evaluation, all patients being seen in person for proper evaluation of safety and efficacy, with a neurological examination including facial sensibility and motility and corneal reflex at 3 months, 6 months and 1 year after the treatment and then regularly once a

year. Every clinical evaluation made by our medical team during the follow-up course was prospectively noted in the database so as to have continuous up-to-date information.

Statistical Analysis

Data were recorded using Microsoft Excel 2000. All statistical analysis was performed using the R software, version 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). The survival R package was used for survival analysis.

First, a descriptive analysis of recorded data was realized among the MS-related TN population.

For the evaluation of outcomes such as initial pain cessation, hypoesthesia and recurrence, time to event was estimated by using the Kaplan-Meier method. A bivariate analysis was then performed to identify predictive factors among the collected variables. For qualitative variables, Kaplan-Meier curves were used to graphically represent survival among the different groups, and they were compared using the univariate log-rank test. For all variables, the effects were estimated and tested by fitting univariate Cox proportional hazards regression models. Proportionality of hazards was assessed graphically by log cumulative hazard plots.

To determine the outcome efficacy, its rate was estimated.

For qualitative variables, the χ^2 test was performed when valid; otherwise the exact Fischer test was used. All tests were 2-sided, and p values of less than 0.05 were judged to be significant.

Table 1. Preoperative general assessment

Variable	Patients, n (%)
Gender	
Male	23 (53.5)
Female	20 (46.5)
Side of pain	
Right	21 (48.8)
Left	22 (51.2)
Pain distribution	
V2	7 (16.3)
V2 and V3	16 (37.2)
V3	13 (30.2)
V1 and V2	2 (4.6)
V1–3	3 (6.9)
V1	2 (4.6)
V1 and V3	1 (2.3)
Typical pain	36 (83.7)
Atypical pain	7 (16.3)
Dead	2 (4.6)
Preoperative MRI vascular conflict other than megadolichobasilar compression	15 (34.9)

Results

General Data

In this series, 23 (53.5%) of all patients were men and 20 (46.5%) were women. The median age was 57.2 years (range 36.1–82.6). The median duration of symptoms was 72 months (range 2–390). The median follow-up period was 53.8 months (range 12–157.1). Table 1 shows a preoperative assessment of our population in terms of clinical evaluation.

Pain was slightly predominant on the left side in 22 patients (51.2%) compared to on the right side in 21 patients (48.8%). Only 2 patients (4.6%) had bilateral pain. Pain was predominantly distributed in the V2 and V3 dermatome of the trigeminal nerve (37.2%), followed by V3 (30.2%), V2 (16.3%), V1 and V2 and V3 (6.9%), V1 (4.6%), V1 and V2 (4.6%), and V1 and V3 (2.3%).

Two patients (4.6%) died but were not excluded from the study as they had had at least 1 year of follow-up at the time of their death.

Preoperative MRI revealed the presence of a vascular conflict in 15 cases (34.9%).

Surgery had previously failed in 21 patients (48.8%), 7 (16.3%) of whom had only had 1 previous intervention, 8 (18.6%) had had 2 previous surgeries and 6 (13.9%) had had 3 or more previous surgeries. The preoperative technique used was radiofrequency lesion in 11 (25.6%) patients, balloon microcompression in 10 (23.2%), microvascular decompression in 3 (7%) and glycerol rhizotomy in 1 (2.3%) patients, respectively (table 2).

Seventeen patients (39.5%) had preoperative sensory disturbances, which was severe in 2 cases (4.7%).

Medical and surgical treatment had failed in the majority of our patients.

Gamma Knife surgery was the first surgical procedure in 22 patients (51.2%).

Initial Pain Cessation

Thirty-nine patients (90.7%) had initial pain cessation in a median time of 30 days (range 0–90). The initially pain free actuarial rate at 15 days, 1, 2 and 3 months was 44.2, 58.1, 81.4 and 90.7%, respectively, and remained stable till 12 months (fig. 1).

The age at the time of GKS ($p = 0.09$), the side of the pain ($p = 0.37$), bilaterality of the pain ($p = 0.16$), the number of dermatomes in which the pain presented ($p = 0.367$), the time elapsed till treatment onset ($p = 0.32$), the topography of the pain ($p = 0.91$ for V1, 0.62 for V2 and 0.53 for V3), previous surgery ($p = 0.4$) and previous side effects ($p = 0.49$) were not statistically significant.

The preoperative neurovascular conflict was statistically significant with a positive predictive value, with a p value of 0.03 (hazard ratio of 0.47 and confidence interval between 0.24 and 0.94).

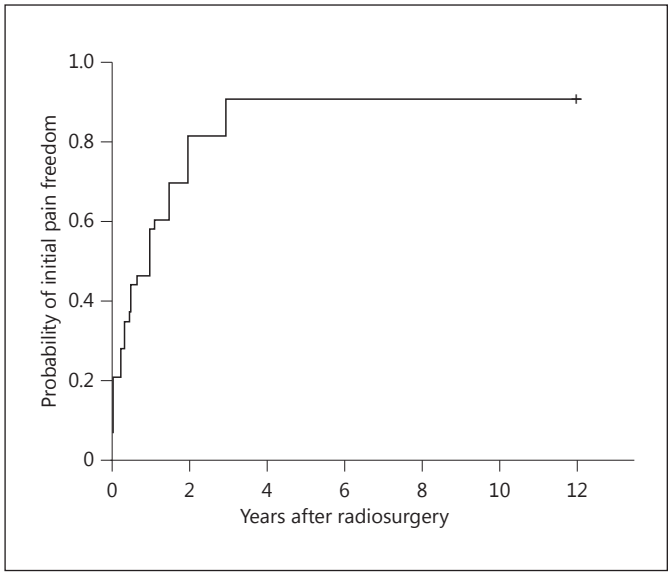

Fig. 1. Kaplan-Meier estimate of the probability of initial pain freedom after GKS.

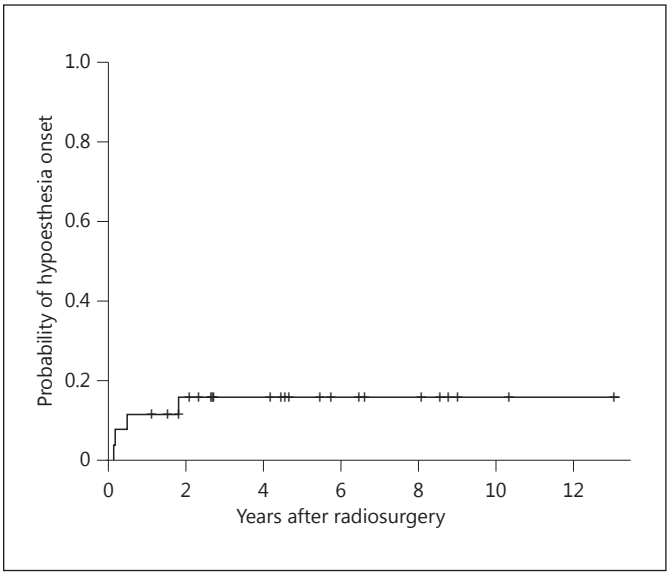

Fig. 2. Kaplan-Meier estimate of the probability of hypoesthesia onset after GKS.

Table 2. Preoperative surgical assessment

Variable	Patients with TN, n (%)
No prior surgery	22 (51.2)
Prior surgery	21 (48.8)
1	7 (16.3)
2	8 (18.6)
≥3	6 (13.9)
Type of prior surgery	
Radiofrequency lesion	11 (25.6)
Balloon microcompression	10 (23.2)
Microvascular decompression	3 (7)
Glycerol rhizotomy	1 (2.3)
Side effects from prior surgery	17 (39.5)
Facial sensibility before GKS	
Normal	26 (60.5)
Slight hypoesthesia	15 (34.9)
Severe hypoesthesia	2 (4.7)
Anesthesia	0

Sensory Dysfunction after GKS

Four patients (16%) without preoperative hypoesthesia developed facial numbness after GKS (fig. 2). The hypoesthesia actuarial rate at 0.5, 1 and 2 years was 11.5, 11.5 and 16%, respectively, and it remained stable till 12 years with a median delay of onset of 6 months (range 2–22). No patient reported a bothersome hypoesthesia. They all considered that their quality of life improved after GKS and that the sensory dysfunction was a good trade-off for pain relief. No case of anesthesia dolorosa was found after GKS.

The gender ($p = 0.31$), age ($p = 0.26$), time elapsed till treatment onset ($p = 0.16$), previous surgery ($p = 0.317$), preoperative neurovascular conflict ($p = 0.13$) and the numbers of territories involved in the pain ($p = 0.65$) were not statistically significant.

The topography of pain within the V1 dermatome was associated with a higher risk of numbness, with a p value of 0.08 (hazard ratio 5.6).

No patients developed a trigeminal motor deficit or any other cranial nerve deficit after GKS.

Recurrent Pain and Salvage Therapy

Twenty-four patients (61.5%) experienced at least 1 recurrence after the GKS treatment. The median time to recurrent pain was of 16 months (range 1.6–146.7).

Because of recurrent medically refractory pain, 22 (51.2%) patients required further surgeries (for postoperative assessment, see table 3). Ten patients (23.2%) required 1 surgical procedure compared to 8 (18.6%) with 2 procedures and 4 (9.3%) requiring at least 3 surgeries. In our unit the most common intervention after failed GKS was balloon microcompression, performed in 16

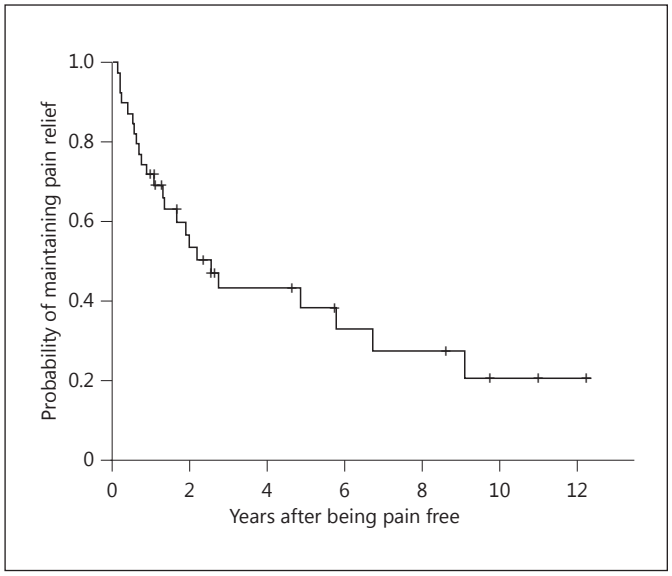

Fig. 3. Kaplan-Meier estimate of the probability of maintaining pain relief.

Table 3. Postoperative global assessment

Variable	Patients with essential TN, n (%)
Initially pain free	39 (90.7)
Post-GKS sensory dysfunction	4 (16)
Mild	4 (100)
Severe	0
BNI facial hypoesthesia (GKS-related) scale	
No facial numbness	22 (84)
Mild facial numbness	4 (16)
Facial numbness, somewhat bothersome	0
Facial numbness, very bothersome	0
Recurrence of pain	24 (61.5)
Additional treatment after GKS	22 (51.2)
1	10 (23.3)
2	8 (18.6)
≥3	4 (9.3)
Balloon microcompression	16 (37.2)
Radiofrequency lesion	5 (11.6)
Second GKS	2 (4.7)
Cortical stimulation	2 (4.7)
Microvascular decompression	0
Glycerol	0

(37.2%) patients, followed by radiofrequency lesion in 5 (11.6%) cases, and a second GKS and cortical stimulation in 2 cases each (4.7%).

The actuarial probability of maintaining pain relief without medication at 6 months, 1, 2, 3, 5, 7 and 10 years, respectively, was 87.2, 71.8, 53.6, 43.1, 38.3, 27.4 and 20.5% and remained stable till 12 years (fig. 3).

Age (p = 0.64), the number of dermatomes involved in the trigeminal pain (p = 0.97), the side (p = 0.11), gender (p = 0.68), bilaterality (p = 0.42), atypical pain (p = 0.21), previous surgery (p = 0.73), postoperative GKS hypoesthesia (p = 0.43) as well as the time elapsed till treatment onset were not statistically significant.

Results at Last Follow-Up

The results of the last follow-up showed a good outcome in 41 patients (95.3%) in the BNI classification, in 36 (83.7%) in the Burchiel classification and in 41 (95.3%) in the Regis classification (table 4).

Table 4. Results at the last follow-up

	BNI classification	Burchiel classification	Regis classification
Good result	41 (95.34%)	36 (83.72%)	41 (95.34%)
Poor result	2 (4.65%)	7 (16.27%)	2 (4.65%)

Discussion

The incidence of MS-related TN varies from one study to another as follows: 1–2% [18], 2.4% in a large series of 800 patients [19], 4.4% [2], 5.1% [12], and 6.3% [10]. In our population, the incidence rate was 7.73% (57 patients), which is within the range presented in the current literature.

TN is usually caused by demyelination of trigeminal sensory fibers within either the nerve root or, less commonly, within the brainstem [18, 20]. In the case of MS, a plaque of demyelination encompasses the root entry zone of the trigeminal nerve in the pons [21]. Additionally, several studies have also described the association of a neurovascular conflict in a minority of patients [4, 22–24]. Love and Coakham [20] demonstrated that demyelination is found to extend along the proximal part of the trigeminal nerve root and, in some cases, right up to its junction with the peripheral nervous system. Some other findings were also reported: the astrocyte processes are usually more numerous and widely distributed within the regions of demyelination; lipid-laden macrophages are present as well as juxtaposed axons and variable numbers

Table 5. Main series of the literature with regard to the role of GKS in the treatment of TN secondary to MS

Authors	Patients, n	Median/ mean age, years	Dose maximum, %			DE, mm	Median FU, months	Patients, %			
			<70 Gy	70–80 Gy	>80 Gy			without pain	>90%	side effects	recurrence
Tuleasca et al., 2014 (current study)	43	57.2 (36.5–82.6)	0	28	72	median 8 (5.7–14.7)	53.8 (12–157.1)	90.7	90.7	16	61.5
Weller et al. [11], 2013	35	62 (39–86)		median 90 (80–90)		near REZ retrogasserian	39 (3–97)	35	88	39	–
Diwanji et al. [8], 2010	13	–		median 75 (70–80)		REZ	67 (13–96)	42	57	7	–
Zorro et al. [12], 2009	37	59 (38–74)		median 80		2–8	56.7 (6–174)	62.1	97.3	5.4	37.8
Rogers et al. [10], 2002	15	–		12	3	REZ	mean of 17 (6–38)	–	80	13	33.3
Huang et al. [9], 2002	7	51 (40–63)		5	2	REZ	28 (13–38)	–	100	57.1	14.3

Figures in parentheses indicate minimum and maximum values. DE = distance from the emergence; FU = follow-up; REZ = root entry zone.

of thinly myelinated fibers, both within and immediately adjacent to the regions of demyelination.

Several articles discussed the role of GKS in the armamentarium of treatment for MS-related TN, either taking this case separately (table 5) or discussing it in the global context of CTN.

Huang et al. [9] analyzed 7 patients with TN related to MS from a larger group of 50 patients. Their median follow-up in this series was 28 months. All 7 patients showed excellent responses to GKS. The rate of complication was relatively high, with hypoesthesia found in 4 patients (57.1%). The recurrence rate was low, with only 1 case (14.3%). Interestingly, they report that the patient who had a recurrence also required the longest time to initial response (5 months) and the longest time to complete resolution of pain (8 months).

Rogers et al. [10] reported a series of 15 patients with a mean follow-up of 17 months. Twelve patients (80%) experienced pain relief after the procedure. Two patients (13%) developed facial numbness and also experienced complete pain relief. Five patients (33.3%) experienced a recurrence and were retreated with the same procedure and target, but with a lower maximal dose. They all improved further.

Zorro et al. [12] evaluated the outcomes for 37 patients with a median follow-up of 56.7 months (range 6–174). Complete pain relief was found in 23 patients (62.1%) immediately after the GKS and in 36 (97.3%) at some point in their course of treatment, respectively. The complication rate was 5.4%. The probability of maintaining pain relief after GKS was 82.6% at 1 year, 73.9% at 3 years and 54% at 5 years. In this paper, an important number of patients with MS-related TN (11 patients, 29.7%) had bilateral pain. As underlined before, this fact had also been stated by other studies [25, 26].

Recently, Jeremy Rowe (in Loescher et al. [27]) published a paper containing an analysis of 72 patients treated for TN (58 cases of CTN and 14 cases of secondary TN) in the National Center for Stereotactic Radiosurgery in Sheffield. They furthermore analyzed 8 patients with TN secondary to MS. Interestingly, 2 of these 8 patients had been treated bilaterally (on separate occasions). Of these 8 patients, 3 (37.5%) were pain free and 6 (75%) were very satisfied. In secondary trigeminal neuralgia (MS included), the hypoesthesia rate was 29%. The rate of recurrence was not further discussed in this subgroup but was reported in the global series.

Weller et al. [11] analyzed a series of 35 cases with a median follow-up of 39 months (range 3–97). If initially the target was the root entry zone, further on in the course of treatments the retrogasserian target was used [15, 16], as reported by our group. The overall initial response (BNI I–III) was 82% in a median time of 42 days (range 2–170). The rate of numbness was rather high (39%); the authors considered this to be related to the use of higher doses and a root entry zone target early in their series.

Some other authors focused on the same topic, but without specific and detailed information: Urgošik et al. [28] stated a poor response rate to GKS, with 4 out of 7 patients having 40–100% residual pain. Only 3 patients experienced complete pain relief and a further recurrence 4–9 months later. Verheul et al. [29] reported 46% pain relief at 5 years in the MS group.

In a recent paper Cruccu et al. [30] referred to the role of surgery versus pharmacotherapy in the management of trigeminal neuralgia in patients with MS, stating that it remains uncertain. Even if in general we can agree with this approach, when dealing with a patient presenting with acute pain, drugs may be sometimes insufficient. If surgery is decided upon, it should follow after an analysis of several factors, especially the medical history of the patient. Even if the probability of recurrence is higher than in the CTN cases, as our data also suggest, we must differentiate between an acute crisis of TN, a MS disease peak or a chronic TN. The authors found no evidence of criteria based on which surgeries should be chosen and performed. Most authors recommend gasserian ganglion procedures unless a vascular compression is identified. Even in this former case some authors suggested less efficacy and increased side effects for MS-related TN cases, e.g. Broggi et al. [31] and Eldridge et al. [32] for microvascular decompression, Kanpolat et al. [5] for radiofrequency lesioning and Kondziolka et al. [6] for glycerol rhizotomy. This is probably related to a different physiopathological context, disease related.

Conclusions

The current series of 43 cases with more than 1 year of follow-up is the largest in the literature, with a very long-term follow-up. In our experience, GKS proved to be safe and effective for treating TN due to MS. The initial rate of pain cessation was high (90.7%), with a low rate of numbness of 16%, never bothersome or disabling; additionally, no anesthesia dolorosa was found. The rate of recurrence was high (61.5%), related to this specific clinical entity.

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